

Efforts toward rapid construction of the cortistatin A carbocyclic core *via* enyne-ene metathesis†

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Received 17th March 2010, Accepted 4th May 2010

First published as an Advance Article on the web 24th May 2010

DOI: 10.1039/c004275g

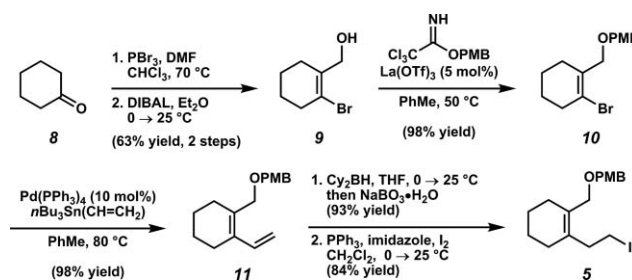
Our efforts toward the construction of the carbocyclic core of cortistatin A *via* an enyne-ene metathesis are disclosed. Interestingly, an attempted S_N2 inversion of a secondary mesylate in our five-membered D-ring piece gave a product with retention of stereochemistry.

The discovery of novel anti-angiogenic agents has become an active area of drug therapy research given their therapeutic applications in the treatment of cancer, autoimmune diseases, macular degeneration, as well as other diseases.¹ A series of unique *abeo*-9(10,19)-androstane-type steroidal alkaloids were isolated from the marine sponge *Corticium simplex* in 2006 and 2007,² some of which possessed significant anti-angiogenic activity. The most potent member, cortistatin A (**1**) demonstrated highly selective growth inhibition of human umbilical vein endothelial cells (IC_{50} = 1.88 nM, selectivity index > 3000) with relatively no general toxicity toward other cell types. The biological activity, as well as the intriguing molecular structure of **1**, have led to several total syntheses³ and efforts toward the construction of the cortistatin A core.⁴

In our approach to the synthesis of cortistatin A (**1**), we envisioned that the [6,7,6,5] core could arise *via* an intramolecular tandem enyne-ene metathesis (Scheme 1).⁵ To examine the feasibility of such a step, we focused on the synthesis of alkynyl

diene **4** as a model precursor for the key enyne-ene metathesis to give pentacyclic model diene **2**. Alkynyl diene **4** could arise from alkyl iodide **5** and nitrile **6**. Nitrile **6**, in turn, could be derived from ketone **7**, which has been synthesized in enantiopure form,⁶ thus providing a direct route for an asymmetric synthesis of the cortistatin A carbocyclic core.

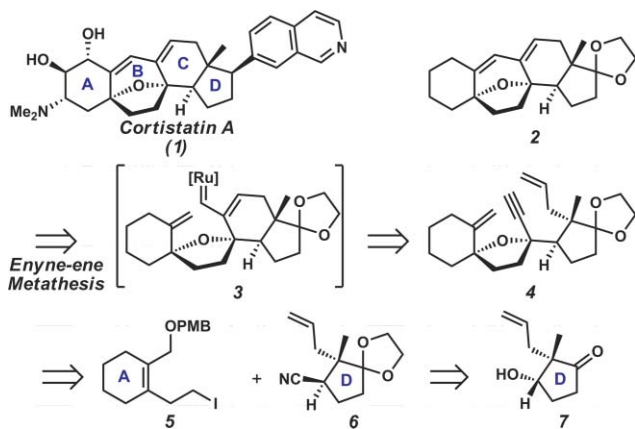
Our synthesis of the A-ring portion of cortistatin A commenced from cyclohexanone **8**, which was converted to the allylic alcohol **9** through treatment with PBr_3 and DMF followed by a DIBAL reduction of the resulting aldehyde (Scheme 2).⁷ PMB protection of the allylic alcohol yielded ether **10**, which was coupled to vinyltributylstannane to afford diene **11**. Hydroboration of diene **11** and subsequent exposure of the resultant primary alcohol to triphenylphosphine and iodine produced iodide **5**.



Scheme 2

With the A-ring precursor **5** in hand, we set out to make the D-ring portion in an asymmetric manner (Scheme 3). Treatment of dione **12** with baker's yeast provided a 9:1 mixture of chromatographically separable alcohols **7** and **13**.⁵ We envisioned that subjecting the major product alcohol **7** to S_N2 displacement conditions would install the final carbon of the D-ring moiety and set the desired absolute and relative stereochemistry. However, mesylation of alcohol **7** followed by treatment with potassium cyanide in DMSO surprisingly afforded nitrile **15**, a product with net retention of stereochemistry at C(14). This unexpected result was confirmed *via* NOESY correlations of alcohols **7** and **13** and nitrile **15**, and by X-ray diffractometry of crystalline compounds derived from alcohol **7** and nitrile **15**.⁹ A possible explanation for this unexpected outcome is that the mechanism proceeds *via* oxetane **16**, which is postulated to arise from reversible cyanohydrin formation of mesylate **14**. Ring cleavage by nucleophilic attack of cyanide at C(14) of oxetane **16** would ultimately afford nitrile **15**.

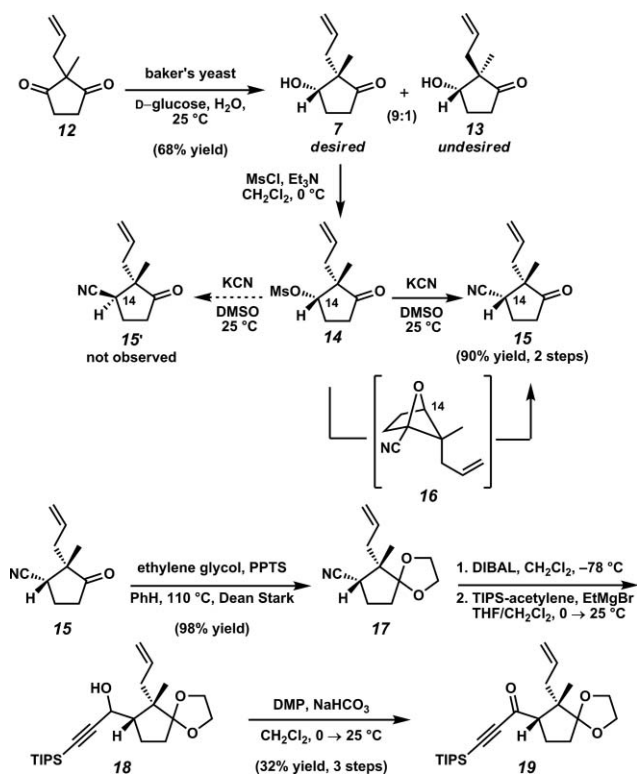
Despite this unusual result we wished to continue the synthesis of the model system due to our interest in testing the enyne-ene metathesis. To advance ketone **15**, we protected the ketone as the acetal to give **17**. Nitrile **17** was then reduced to the aldehyde



Scheme 1

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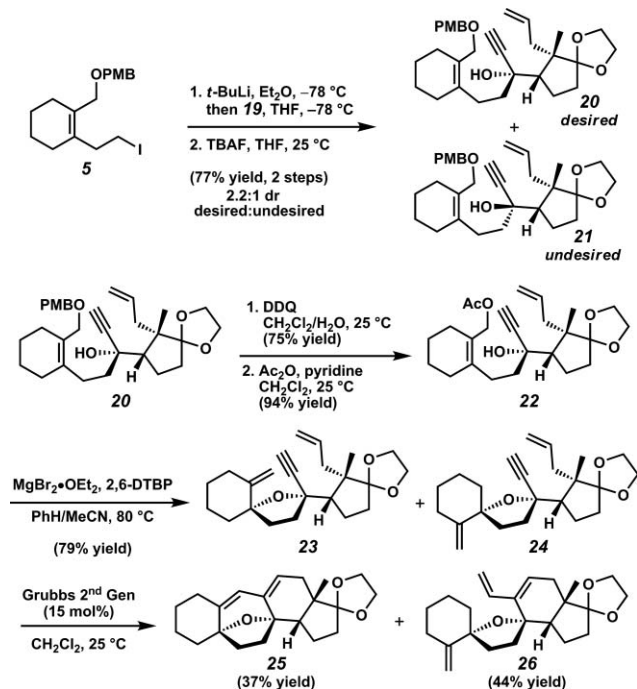
† Electronic supplementary information (ESI) available: General experimental procedures, characterization data, NMR, and IR spectra. See DOI: 10.1039/c004275g



Scheme 3

and after treatment with TIPS–acetylene and EtMgBr, afforded alcohol **18** as a mixture of diastereomers. Alcohol **18** was oxidized with Dess–Martin periodinane (DMP) to give ketone **19**.

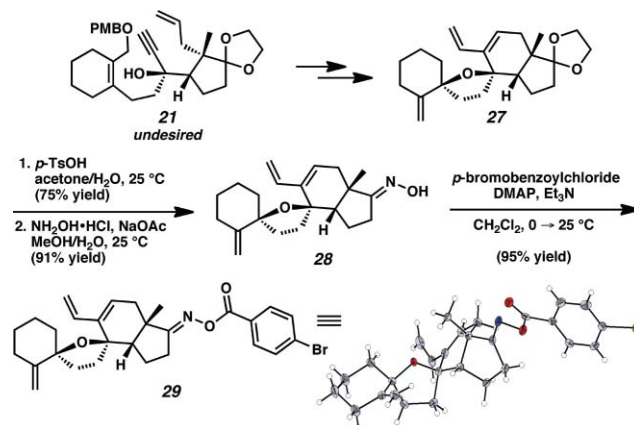
With our A-ring (**5**) and *epi*-D-ring (**19**) precursors in hand, we then coupled the two together by treating vinyl iodide **5** with *t*-BuLi and adding the resultant lithio species to ketone **19** (Scheme 4).



Scheme 4

Subsequent TIPS cleavage with TBAF gave a 2.2 : 1 mixture of the desired alcohol **20** (Felkin-Anh product) and the undesired alcohol **21**. After separation by column chromatography, PMB ether **20** was converted to allylic acetate **22**. Treatment of **22** with MgBr₂ gave a 1 : 1 mixture of substituted tetrahydrofurans **23** and **24**,¹⁰ which were inseparable by column chromatography. Nonetheless, subjection of the mixture of **23** and **24** to Grubbs second-generation catalyst produced the desired enyne-ene metathesis [6,7,6,5]-core **25** in 37% yield and the enyne metathesis product **26** in 44% yield.

We planned to establish the absolute and relative stereochemistry of our metathesis products *via* derivatization to give compounds suitable for X-ray crystallography analysis. Attempts to convert the [6,7,6,5]-core **25** or the enyne product **26** to crystalline compounds were not successful. However, we were able to derivatize the undesired alcohol **21** by proceeding through a similar route as outlined in Scheme 4 for **20** to ultimately afford enyne product **27**. Enyne product **27** was then transformed to oxime **28**, which was acylated with *p*-bromobenzoylchloride to furnish **29**, a compound that was amenable to X-ray diffraction (Scheme 5). As a result, we were able to assign the relative and absolute stereochemistry of [6,7,6,5]-core **25** and enyne product **26**.



Scheme 5

Herein, we have established the enyne-ene metathesis as a rapid method for the construction of the carbocyclic core of cortistatin A. We have also reported an unusual reaction in which an attempted S_N2 displacement of a secondary mesylate on our five-membered D-ring piece gave product with retention of stereochemistry. Further studies directed toward the synthesis of cortistatin A and related analogs are underway and will be reported in due course.

Acknowledgements

C. B. thanks the Schweizerischer Nationalfonds (SNF) for a fellowship. This publication is based on work supported by Award No. KUS-11-006-02, made by King Abdullah University of Science and Technology (KAUST). Additionally, the authors thank Abbott, Amgen, Boehringer-Ingelheim, Bristol-Myers Squibb, Merck, Sigma-Aldrich and Caltech for generous funding. Mr Lawrence Henling and Dr Michael Day are gratefully acknowledged for X-ray crystallographic structural determination. The

Bruker KAPPA APEXII X-ray diffractometer was purchased via an NSF CRIF:MU award to the California Institute of Technology, CHE-0639094. Dr David VanderVelde and Dr Scott Ross are acknowledged for NMR assistance. Dr Scott Virgil is acknowledged for helpful discussions.

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- 8 The enantiomeric excess of the benzoate derivative of alcohol **7** was determined by chiral HPLC to be >99% ee. See the ESI for details†.
- 9 See the ESI for details†.
- 10 Determined by ¹H NMR. See the ESI for details†.
- 11 The percentage probability chosen for the ellipsoids is 50%.